

Water is the most precious resource for life. It constitutes 70% of the human body weight and is the "cradle" for its growth since conception. It is the fundamental element to preserve and promote human well-being and health in all aspects and at all stages of life. Balneology is a medical discipline included by the World Health Organization (WHO) in the field of complementary and integrated medicine that uses natural methods of treatment, prevention and rehabilitation. Founded in 1937, FEMTEC (World Federation of Hydrotherapy and Climatotherapy) represents one of the main federations of Thermal Medicine and Hydrotherapy worldwide, coordinating the activity of the institutions of the sector in over 30 countries and collaborating with WHO, ISMH (International Society of Medical Hydrology), as well as with Universities and Ministries of Health of the different Member States. FEMTEC is strongly committed to promoting research in the field of balneology, according to the most modern methods of investigation. The recent COVID-19 pandemic has posed important scientific questions, to date only partially clarified. One of the aspects that have emerged is the fundamental role of the immune system in prevention, therapy and rehabilitation related to the COVID-19 infection. FEMTEC has therefore questioned the role of balneotherapy in improving human immune function. The federation has therefore decided to release a document to provide reliable scientific data based on specific methodological criteria on the role of balneotherapy in human health and, more specifically, in improving the immune response. The Authors, Dr. Maria Chiara Maccarone, Dr. Giacomo Magro and Dr. Anna Scanu, coordinated by Prof. Stefano Masiero, Director of the Rehabilitation Department of the University of Padua (Italy) and President of the Femtec Commission for Physical Therapy, have carried out a thorough research and critical analysis of the existing literature on the subject from which emerges a picture of undoubted interest that not only seems to confirm the important role of balneotherapy in the prevention of certain diseases, but also opens interesting perspectives in other fields of research. In recent years there has increased interest in the use of preclinical models (in vitro studies on human or animal samples) to study the biological effects of balneotherapy on inflammation and immunity. Recently, clinical trials and randomized controlled trials have also been developed to study in vivo the effects of thermal medicine on the human immune system. However, the mechanisms through which immersion in thermal water or mud treatments may be useful to improve human immune functions are not yet fully understood. In this paper 30 in vitro studies on human and animal samples published between 1997 and 2020 on the effects of balneotherapy on the immune system in models of dermatological, musculoskeletal and inflammatory diseases have been considered. In addition, 10 clinical studies on healthy populations and patients suffering from arthrosis, ankylosing spondylitis, fibromyalgia and psoriasis have been considered. On human in vitro samples, sulphurous compounds contained in thermal waters have been shown to exert an anti-inflammatory action on psoriatic lesions and arthrocytic chondrocytes. In addition, the same compounds appear to regulate inflammation and immune response in human peripheral blood. Overall, in vitro results demonstrate the anti-inflammatory and immunomodulatory effects of balneotherapy in several human diseases.

Also in vivo, in the cohorts of patients with considered osteoarthritis, balneotherapy has been shown to have anti-inflammatory efficacy, modulating the cytokinic response and modifying the percentage of regulatory T cells in the bloodstream. Following balneotherapy and mud therapy, a reduction in serum levels of pro-inflammatory molecules such as TNF- $\alpha$ , IL-1 $\beta$ , PGE2, LTB4 and C-reactive protein and an increase in anti-inflammatory molecules such as IGF-1 growth factor have been shown. Even in patients with fibromyalgia or ankylosing spondylitis balneotherapy has been shown to influence inflammatory mediators.

In conclusion, studies on in vitro samples could pave the way for scientific progress and future clinical studies could help to identify, in real life and in clinical practice, the effects on the immune system of balneology, further developing this possibility of use of spa treatments.

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